

Invasive endometrial lesion in a patient with mental retardation

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A 46-year-old Caucasian woman with mental retardation experienced discomfort and irregular menstrual bleeding, which had been increasing for 2 years. The physician from her group home sent her to a gynecologist, where a mass prolapsing through the cervix was noted on physical examination. Cervical and endometrial biopsies were done. Both showed polypoid fragments of endometrium with complex hyperplasia with cytologic atypia and squamous metaplasia (*Figure 1*). A computed tomography scan showed the mass in the uterine cavity, but everything else appeared normal. She was referred to a gynecologic oncologist.

The patient had three risk factors for endometrial cancer: obesity (she weighed 210 pounds, and her body mass index was 36 kg/m²), nulliparity, and hypertension. Both her hypertension and a seizure disorder were well controlled with medications. It was unclear if Pap smears had been done in the past.

The probability of endometrial cancer was discussed with her, and she agreed to surgery. Informed consent was obtained through her brother, her legal guardian who also had medical power of attorney. Procedures included exploratory laparotomy, total abdominal hysterectomy, bilateral salpingo-oophorectomy, and bilateral pelvic lymph node dissection.

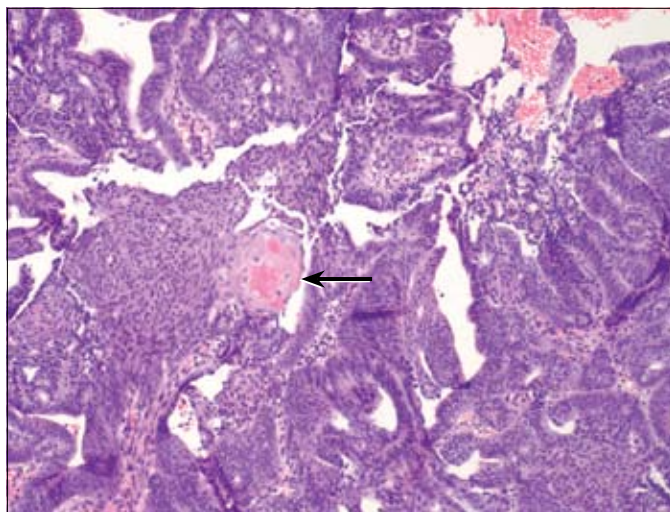


Figure 1. Endometrial curettings. A low-power view demonstrating irregular atypical glands with very little intervening stroma. Squamous differentiation is present (arrow).

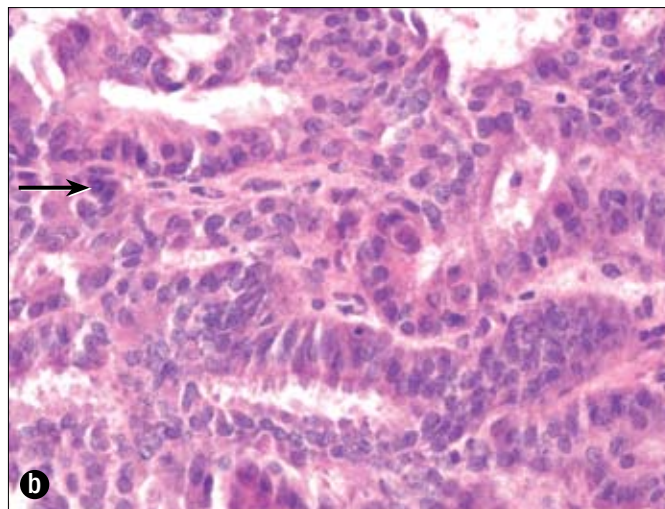
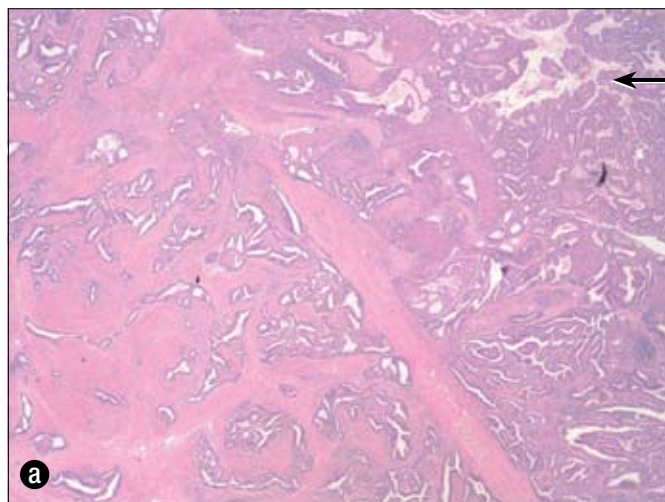


Figure 2. (a) Section of endomyometrium of the hysterectomy specimen, consisting predominantly of irregular atypical glands infiltrating the myometrium. Focus of solid tumor is present. (b) A high-power view of endometrial carcinoma, endometrioid type, FIGO grade 2. Note the irregular atypical glands with back-to-back appearance. The cells are atypical with pleomorphic hyperchromatic nuclei and increased mitotic activity (arrows).

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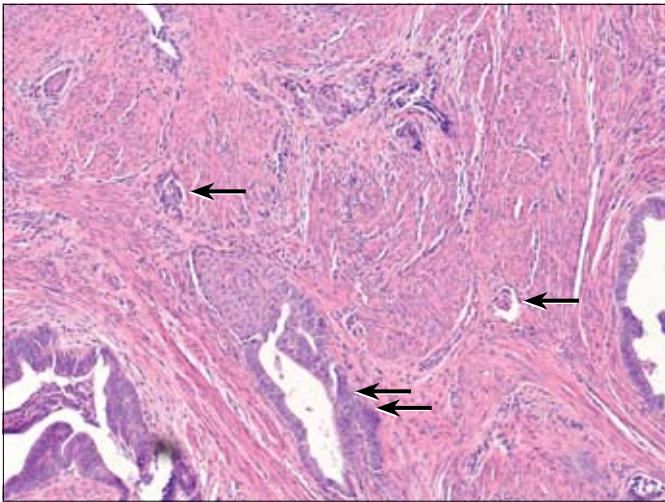


Figure 3. Multifocal lymphovascular invasion present within the myometrium (single arrow). The tumor invades the myometrium (double arrow).

The findings at surgery were a normal appearing uterus, ovaries, and fallopian tubes, with no evidence of obvious disease. The left external iliac vein lymph node appeared pathologically enlarged to 2 cm. The remainder of the pelvic and paraaortic lymph nodes were of normal size, and no other gross abnormalities were seen in the abdomen or pelvis. Clear surgical margins were obtained.

On gross pathological examination, the uterus was 223 g and measured 12.3 × 7 × 5.3 cm. A polypoid tumor, 9.5 × 3.2 × 3.5 cm, was identified, and gross involvement of the lower uterine segment was noted. The cervix and both ovaries were free of disease, both grossly and microscopically, but a right paratubal cyst and left hydrosalpinx were found.

Microscopic examination revealed endometrial adenocarcinoma of the endometrioid type (Figure 2). Myometrial invasion of 18/20 mm of myometrial thickness was present, and the lower uterine segment was involved up to the endocervical junction. In addition, multifocal lymphovascular invasion was present (Figure 3).

A total of 28 lymph nodes were excised from the left pelvic, right pelvic, and paraaortic regions. One lymph node in the left pelvis showed metastatic adenocarcinoma, with the largest focus 1.5 cm (Figure 4).

Estrogen receptor staining (2–3+) was present in 70% of tumor nuclei; progesterone receptor (3+), 75%; and MIB1, 20% and focally 40% to 50%.

SURGICAL STAGING AND OPTIONS FOR FURTHER TREATMENT

Based on the pathological results—most notably, the involvement of one lymph node in the pelvis—the patient’s cancer was stage IIIC, grade 2, using the surgical staging system of the joint International Federation of Gynecology and Obstetrics (FIGO)/American Joint Committee on Cancer (AJCC) (Table). In general, stage III endometrial cancer has a 5-year survival rate of 60%.

Gynecologic oncologists and pathologists have developed useful and accurate models for prognosis of endometrial cancer (1–8). In this case, the positive lymph node, lymphovascular invasion, myometrial invasion, 9 cm tumor size, and lower segment

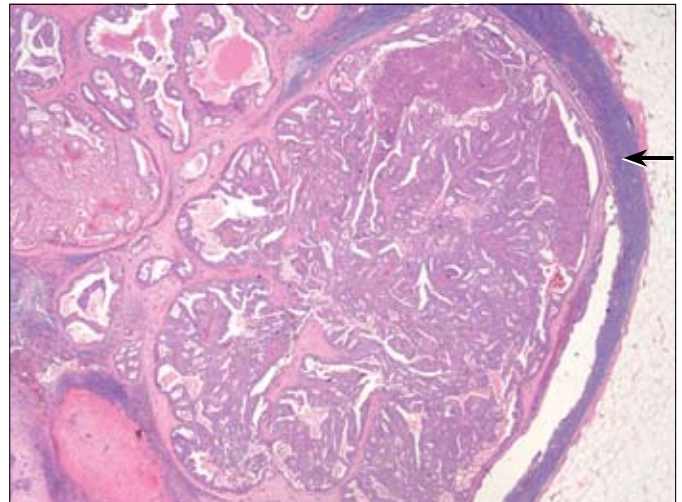


Figure 4. Extensive involvement of the left pelvic lymph node by metastatic endometrial adenocarcinoma. Note the thin rim of lymph node tissue at the periphery (arrow).

involvement were negative prognostic factors, while the positive estrogen and progesterone receptor status were positive prognostic factors. This patient faces a high risk of recurrence, which can be offset with radiotherapy, chemotherapy, or hormonal therapy.

Postoperative radiation therapy for endometrial cancer is used less often today than in the past. One reason relates to the cost-benefit analysis: several randomized studies have demonstrated a reduction in locoregional recurrence but with significant toxicity and no improvement in overall survival (9). At the same time, many of the studies included early stage patients. Some centers have addressed this balance by reserving pelvic and paraaortic radiotherapy for surgically staged patients with a high risk of recurrence, believing that this group is the most likely to benefit (10).

Chemotherapy faces many of the same challenges. A 2007 metaanalysis of 11 randomized controlled trials involving 2288 patients concluded that the intense combination chemotherapy regimens were beneficial: they improved disease-free survival and modestly improved overall survival. However, these regimens were also associated with gastrointestinal toxicity and myelosuppression (11). Two systematic reviews conducted in 2006 that also included hormonal systemic treatment had more guarded conclusions: one referred to a “limited survival advantage” (12) and one summarized by stating: “Overall, randomized evidence on systemic treatment in advanced endometrial cancer is fragmented, and survival benefits for specific regimens are questionable” (13). However, chemotherapy remains standard treatment for patients with metastatic or locally advanced endometrial cancer (10).

Hormonal therapy—natural and synthetic progestins as well as tamoxifen, an antiestrogen—has had good results in defined populations. A metaanalysis showed five studies that correlated response rates with receptor status. In estrogen and progesterone receptor-positive patients, response rates ranged from 26% to 89% (14). The treatment has less toxicity than radiotherapy or chemotherapy. It should be kept in mind that response is dependent on grade—with grade 3 tumors having a response rate only a third that of grade 1 tumors (14).

Table. Staging of cancer of the uterine corpus*

Definition of TNM		TNM	FIGO	Definition
		Primary tumor (T) (Surgical-pathologic findings)	TX	
T0				No evidence of primary tumor
Tis			0	Carcinoma in situ
T1			I	Tumor confined to corpus uteri
T1a			IA	Tumor limited to endometrium
T1b			IB	Tumor invades less than one-half of the myometrium
T1c			IC	Tumor invades one-half or more of the myometrium
T2			II	Tumor invades cervix but does not extend beyond uterus
T2a			IIA	Tumor limited to the glandular epithelium of the endocervix. There is no evidence of connective tissue stromal invasion.
T2b			IIB	Invasion of the stromal connective tissue of the cervix
T3			III	Local and/or regional spread as defined below
T3a			IIIA	Tumor involves serosa and/or adnexa (direct extension or metastasis) and/or cancer cells in ascites or peritoneal washings
T3b			IIIB	Vaginal involvement (direct extension or metastasis)
T4			IVA	Tumor invades bladder mucosa and/or bowel mucosa (bullous edema is not sufficient to classify a tumor as T4)
Regional lymph nodes (N)	NX			Regional lymph nodes cannot be assessed
	N0			No regional lymph node metastasis
	N1		IIIC	Regional lymph node metastasis to pelvic and/or para-aortic nodes
Distant metastasis (M)	MX			Distant metastasis cannot be assessed
	M0			No distant metastasis
	M1		IVB	Distant metastasis (includes metastasis to abdominal lymph nodes other than para-aortic, and/or inguinal lymph nodes; excludes metastasis to vagina, pelvic serosa, or adnexa)
Stage grouping	0	Tis	N0	M0
	I	T1	N0	M0
	IA	T1a	N0	M0
	IB	T1b	N0	M0
	IC	T1c	N0	M0
	II	T2	N0	M0
	IIA	T2a	N0	M0
	IIB	T2b	N0	M0
	III	T3	N0	M0
	IIIA	T3a	N0	M0
	IIIB	T3b	N0	M0
	IIIC	T1	N1	M0
		T2	N1	M0
		T3	N1	M0
IVA	T4	Any N	M0	
IVB	Any T	Any N	M1	
Histopathology—degree of differentiation Cases of carcinoma of the corpus uteri should be grouped with regard to the degree of differentiation of the adenocarcinoma as follows.	G1	5% or less of a non-squamous or non-morular solid growth pattern		
	G2	6% to 50% of a non-squamous or non-morular solid growth pattern		
	G3	More than 50% of a non-squamous or non-morular solid growth pattern		

*Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the *AJCC Cancer Staging Handbook*, 6th ed. (2002) published by Springer Science and Business Media LLC, www.springerlink.com

FIGO indicates Federation Internationale de Gynecologie et d'Obstetrique.

INFORMED CONSENT ISSUES

The National Comprehensive Cancer Network guidelines recommend both chemotherapy and tumor-directed radiotherapy for stage IIIC endometrial cancer (15). However, it is appropriate to consider the patient. She was not independently capable of reviewing her options and giving informed consent; further, she had limited understanding of why these debilitating treatments were necessary. At the same time, the patient went through surgery without complications or difficulties and appeared to understand what was happening. Discussions were held with her family—although it is recognized that families can have different expectations than the patients.

In a panel discussion featuring a scenario in which a mentally ill patient refused treatment for leukemia and her sister, who had power of attorney, insisted on it, several points of view were given (16). An oncologist suggested a 1-week trial of therapy while temporarily halting other interventions that were distressing; such a trial might determine if the therapy was likely to be effective. An ethicist suggested respecting the patient's wishes and seeking hospice care. An attorney noted that courts "refused to accept the premise that incompetent persons must always be subjected to the medical treatments that mentally sound persons ordinarily would choose." Finally, a nurse suggested education of the patient and her sister and professional counseling (16).

All of these insights can be applied in this case. Attempts can be made to educate and counsel the patient and all involved and to use trials with therapy to see how well they are tolerated. Fortunately, hormonal therapy, which has minimal side effects, is also an excellent option for this patient. Ethics and palliative care consultation can be called upon as needed. The patient's ongoing treatment is still pending. She will be seen at routine intervals to rule out a recurrence.

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